REMARKS

Claims 9, 11, 18, 21-23 and 27 are pending. Claims 11, 23 and 27 have been amended. Support for the amendments and can be found throughout the specification including the Drawings and claims as filed originally. No new matter has been added.

Claim Rejections

1) Claims 18, 21-23 and 27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for reasons of record as set forth in the office action mailed February 22, 2006. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

> The Examiner states, "Applicant argues that (1) the specification has demonstrated production of HEK293 cell lines that individually express a chloride channel such as CIC-3, CIC-6 or CIC-7 and these type of cell lines can be used to determine if a compound can selectively block CIC-7 and not the other chloride channels. (2) The examiner has gone beyond what the claimed invention should properly be requiring. Since the claims are directed to methods of for screening, they should be understood as relating to the identification of compounds that have an increased likelihood of being suitable for use in treatment of an osteoclast disorder. Further, the inventors have demonstrated the expression of CIC-7 in osteoclasts and osteoclasts have to secrete an acidic enviroment to achieve resorption. Therefore, it highly likely that compounds that interfere with chloride transport will modulate bone resorption. The specification does not assert that every compound that can block CIC-7 will be useful in treatment, but rather the purpose of the claimed invention was to identify compounds that are worth further investigation for treatment. (3) The rejection with regard to lack of evidence of a role of CIC family channel members other than CIC-7 in osteoclast disorders is moot in view of an amendment directing the claims to only CIC-7. Further, the burden of experimentation in connection with compounds that block CIC-7 is not large and to determine if the identified compound may

be of therapeutic value would only involve routine tasks of exposing osteoclasts to the relevant compound in a bone resorption assay of a known kind by suitable in vivo testing. Applicant's further argue that an article by Schaller et at demonstrates that a compound identifiable using screening methods as described in the specification has in vivo effect in rats in modulating osteclast activity resulting in the prevention of bone loss. Therefore, this paper verified the predictive teaching of the current application.

In response to applicant's arguments, (1) the examiner agrees that compounds that selectively block one channel can be identified. (2) The claims are directed to a screening method to identify compounds for the treatment in an osteoclast disorder, but the applicant has not demonstrated that the screening method works to identify even one compound with potential activity to treat any osteoclast-related disorder. Further, the compound screening assay is conducted in the human embryonic kidney cell line HEK293 cells that recombinantly express CIC-7 and are not related to an osteoclast. Additionally, the applicants have not demonstrated that any osteoclast disorder will be affected by blocking CIC-7. In particular, osteopetrosis results from a defect in CIC-7 that results in its reduced activity and increased bone mass. Therefore, it unclear how a compound that blocks CIC-7 will serve as a potential compound for the treatment of osteopetrosis. Further, in terms of Paget's disease and oncolytic cancer invasion the specification has no provided evidence on how a compound that blocks CIC-7 and modulates bone resorption will result in a treatment for these diseases. (3) The rejection with regard to the other CIC family members is moot due to the applicant's amendment to direct the invention only to CIC-7. The experimentation to determine the ability of compounds to treat any osteoclast-related bone disease is not routine experimentation. The testing would encompass using a valid animal model for every osteoclast-related disorder. Schaller et al demonstrates analysis of the chloride channel inhibitor NS3736 for its ability to inhibit chloride conductance in differentiated osteoclasts and its ability to inhibit bone resorption *in vitro* and in the OVX rat model. Schaller et al further determines which chloride channel may be inhibited by the NS3637 compound by expression pattern analysis of CIC-7 and CLIC1. The expression of CIC-7 on osteoclasts suggests that NS3736 may inhibit CIC-7. Schaller et al does not teach identifying compounds for the treatment of osteoporosis by screening compounds specifically for their ability to block CIC-7 and do not directly demonstrate that NS3736 blocks CIC-7. Therefore, the methods taught by Schaller et al do not teach the steps claimed by the applicant to screen for potential compounds that block CIC-7 and treat osteoclast-related bone disease.

> Claims 18, 21-23 and 27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for reasons of record as set forth in the office action mailed February 22, 2006 and above.".

Applicants respectfully disagree. In the 132 Declaration filed herewith, the inventor Dr. Morten Karsdal explains how an acidification assay usable in a screening method according to the invention gives a positive result for a compound NS3736 which abrogates acidification in HEK cells overexpressing ClC-7. The previously filed reference Schaller et al referred to in the current Office Action demonstrates that the same compound NS3736 is a potent inhibitor of osteoclast mediated bone resorption. It is thereby demonstrated that the screening assay would be capable of identifying NS3736 as a compound with potential activity to treat an osteoclast-related disorder.

The Examiner further argued that '*the compound screening assay is conducted in the human embryonic kidney cell line HEK293 cells that recombinantly express ClC-7 and are not related to an osteoclast.*' The work reported in the Declaration clearly demonstrates that this is not an obstacle to the working of the invention. Moreover, it should be recognised that the recombinant HEK cells are 'related to an osteoclast' in that they have been engineered to express ClC-7, thus conferring on them a property which strongly characterizes osteoclasts.

The Examiner has further stated that *'the applicants have not demonstrated that any osteoclast disorder will be affected by blocking ClC-7'*. That statement is ambiguous and the sense in which it is intended is not presently understood by the Applicant. It could mean that it is alleged that the applicants have not demonstrated that there is any (even one) osteoclast disorder that will be affected by blocking ClC-7. If that was intended, then the Declaration clearly shows that it is highly probable that conditions characterised by excessive bone resorption will be affected by blocking ClC-7, as compound NS3736 is demonstrated both to block ClC-7 and to inhibit bone resorption by osteoclasts. Furthermore, the Examiner has previously acknowledged (Office Action of

22nd February 2006, page 9) that Kornack et al demonstrated a correlation between loss of the ClC-7 chloride channel (in osteoclasts) and resulting osteopetrosis, which would reflect a decrease in bone resorption causing the balance of the simultaneous processes of bone resorption by osteoclasts and bone formation by osteoblasts to shift in favor of net bone formation.

Alternatively, the Examiner may here be using the word 'any' in the sense of 'any chosen' or 'every', implying that it is necessary that the screening method identify compounds having potential utility in treating every disease that is related to a disorder in osteoclasts. This interpretation is supported by the Examiner's specific contention that the screening method will not be expected to identify compounds useful in treating osteopetrosis if that disease is caused by a defect in ClC-7 in osteoclasts.

The Examiner will note that in this amendment, reference to osteopetrosis is deleted from claim 11 and claim 27. It is not a requirement of claim 18 that compounds passing the screen should be useful in treating every different osteoclast disorder mediated disease. No such assertion arises from the wording of the claim or is needed for utility. Clearly, the claim only requires that there should be some osteoclast related bone disease to which any single given compound passing the screen should be relevant. Not all compounds passing the screen need to be relevant to the same disease and none needs to be relevant to all such diseases.

The Examiner has further commented that '*in terms of Paget's disease and oncolytic cancer invasion the specification has provided no evidence on how a compound that blocks ClC-7and modulates bone resorption will result in a treatment for these diseases.*'

A treatment does not of course have to be curative, it may only have the effect of slowing rather than reversing the progress of a disease or ameliorating its symptoms. Neither is it necessary to the concept of a treatment that a single medicament should

bring about an improvement alone rather than in conjunction with other known treatments. Paget's disease is characterized by anomalous bone turnover. Bone is resorbed and is replaced by abnormal bone. Clearly, reduction of the amount of bone resorption will have a part to play in treatment and the standard treatments for Paget's disease include treatments with agents that restrict bone resorption and which for that reason are also used in treating osteoporosis. These include bisphosphonates and calcitonin. There is therefore every reason to expect that a new agent for restricting the bone resorbing action of osteoclasts will have an effect in the treatment of Paget's disease.

Oncolytic cancer invasion (secondary bone cancer) is known to be mediated by cancer cells emanating from a non-bone primary cancer secreting chemical signals that attract and stimulate osteoclasts to carve out space in bone within which the cancer cells can grow or from which the cancer cells derive nutrients. This causes hypercalcaemia as well as pain, fracture risk and other symptoms. Again, a standard treatment for this condition is to administer bone resorption reducing agents including bisphosphonates to restrict the action of the osteoclasts. See for instance http://www.cancerbackup.org.uk/Cancertype/Bonesecondary/Treatment/Bisphosphonates

Here again, it is immediately predictable that new compounds that prevent the action of osteoclasts in resorbing bone will have potential to ameliorate the progress of secondary bone cancer that acts through the over-stimulation of osteoclasts.

The Examiner goes on to state that '*The experimentation to determine the ability of compounds to treat* ***any*** *osteoclast–related bone disease is not routine experimentation. The testing would encompass using a valid* ***animal*** *model for* ***every*** *osteoclast related disorder.*' Here, the Examiner does seem to be using 'any' to mean 'every'. We submit that this (a)clearly goes beyond what the claims require and (b) is legally unsound.

Since it is established to be fundamental to the bone resorbing ability of osteoclasts that they can acidify a compartment on the bone surface within which resorption occurs and since it has been established in the invention that the action of ClC-7 is of fundamental importance to the process by which osteoclasts produce acidification of the compartment, it clearly follows that preventing acidification via ClC-7 will inhibit bone resorption by osteoclasts. This has been experimentally demonstrated by the work described in the Declaration and by Schaller et al.

Claim18 is satisfied if the screening reveals potential utility for treating 'an osteoclast related bone disease' and does not require that one compound or several compounds between them should have utility in treating every osteoclast related disease. Accordingly, even if it were the case that an animal model would be needed (see below), it could not be the case that animal models for all osteoclast related diseases could be required.

Secondly, there is no requirement imposed by the claim for possessing a disease model (whether in vitro or animal in nature) at all. The claim only requires the identification of compounds which are potentially active in treating disease. The identification of compounds with potential activity is complete and done at the end of the screen. All compounds passing the screen have an increased potential vis a vis the totality of unscreened compounds. Thus, compounds with potential have already been identified without any further testing being done.

Even if it were thought to be necessary that some further investigation of the actual utility of successfully screened compounds should be made, there is no legal requirement that this should be an animal model. Further screening against osteoclasts in vitro to determine the ability of the successfully screened compounds in inhibiting bone resorption (as in Schaller et al) would be entirely sufficient.

Moreover, for the major bone resorption disease conditions such as osteoporosis, animal models are well established and much used.

The Examiner further argues that '*Schaller does not teach identifying compounds for the treatment of osteoporosis by screening compounds specifically for their ability to block ClC-7 and do not directly demonstrate that NS3736 blocks ClC-7.*'

The Declaration filed herewith demonstrates that NS3736 blocks ClC-7 and could be identified as doing so by the claimed screen. It is thereby confirmed that taking the steps described in the application does indeed produce a screen for compounds active in blocking ClC-7 and that NS3736 blocks ClC-7.

Applicants accordingly submit that the description provided in the application clearly demonstrates possession of the invention as claimed and is fully enabling thereof. Applicants respectfully request reconsideration.

2) Claims 11 and 23 are rejected under 35 U.S.C. 112, second paragraph for particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

> The Examiner states, "Claim 11 recites the limitation "wherein the osteoclast bone disease" in line 2. There is insufficient antecedent basis for this limitation in the claim.
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> Claim 23 recites the limitation "one or more chloride channels of the ClC family" in lines 3, 5 and 6. There is insufficient antecedent basis for this limitation in the claim. In particular, the independent claim 18 has been limited to the ability of compounds to block ClC-7 only.".

Applicants have amended claims 11 and 23 to correct the insufficient antecedent basis and, thereby obviate the rejections.

3) Claim 23 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim.

> The Examiner states, "Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claim directed to measuring the ability of compounds to block one or more chloride channels and is dependent on claim 18 which limits the chloride channel to CIC-7.".

Applicants have amended claim 23 to remove the objection by reference to ClC-7 in the claim, thereby obviating the basis for objection.

CONCLUSION

Applicants submit that all claims are allowable as written and respectfully request early favorable action by the Examiner. Applicant's representative would like to discuss this case with the Examiner to learn if any outstanding issues remain after consideration of this Amendment. If the Examiner believes that a telephone conversation with Applicants' attorney would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney of record. Should it be required, the Applicants conditionally petition for a extension of time to provide for the possibility that such a petition has been inadvertently overlooked and is required. As provided below, charge Deposit Account No. **04-1105** for any required fee.

Respectfully submitted,

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